

## REMARKS

Claims 1-6, 11, 12, 14, 19, 20, 32-51, 54-56, 58, and 59 are currently pending. Claims 32-40, 44-51, 54-56, 58, and 59 are withdrawn from consideration at this time. Claims 1-6, 11, 12, 14, 19, 20, and 41-43 are rejected. Each of the rejections levied in the Office Action is addressed individually below.

### Rejection of claims 1-12, 14, 19-22, and 41-43 under 35 U.S.C § 103(a).

Claims 1-12, 14, 19-22, and 41-43 are rejected under 35 U.S.C § 103(a) as unpatentable over Cervigni *et al.*, in view of U.S. Patent No. 5,958,398 by Papisov (“the ‘398 patent”), U.S. Patent No. 5,612,037 by Huebner (“the ‘037 patent”), and G. Hermanson, Preparation of Liposome Conjugates and Derivatives, Bioconjugate Techniques, pp. 552-589, (“Hermanson”). Specifically, the Examiner asserts that “a conjugate of polyacetals or polyketals with a modifier through an oxime-containing liker [sic] are taught, suggested and motivated from the combined references.” Applicant respectfully disagrees.

Cervigni teaches conjugation of peptides to aldehyde-containing compounds such as carbohydrates, lipids, peptides, steroids, and PEG. As acknowledged by the Examiner, Cervigni does not teach or suggest a conjugation to polyacetals or polyketals. The Examiner takes the position that the combination of the method of Cervigni with the polyacetals of the ‘398 patent teaches the presently claimed invention. Applicant respectfully submits that the Examiner is mistaken.

The present claims recite biodegradable biocompatible polyacetals or polyketals conjugated to modifiers via oxime linkages. Assuming for the sake of argument that one of ordinary skill in the art having read Cervigni would want to make such conjugates, the application of the Cervigni methods to the polyacetals of the ‘398 patent would not achieve the claimed invention. The *biodegradable biocompatible* polyacetal exemplified by the ‘398 patent

is poly(hydroxymethylethylene hydroxymethylformal), or PHF (see Examples 1 and 2 of the '398 patent). It is known in the art that the stability of the PHF main chain is pH-dependent (see Papisov, M.I., *ACS Symposium Series*, **786**, 301-314, 2001, submitted herewith as Appendix A). Cervigni exemplifies very harsh (*i.e.*, pH 3 for 120 hours) conditions for conjugation (see caption of Scheme 2 and 2<sup>nd</sup> paragraph of Experimental Procedure) that would cause nearly complete hydrolysis of the PHF main chain (see Papisov, Figure 4, PHF after 4 days incubation at pH 3).

One of ordinary skill would realize that under these conditions the polyacetals of the '398 patent would be *essentially depolymerized* and a conjugate product would not be formed at all or would be of very low molecular weight. Whatever would be formed by such a reaction would neither anticipate nor render obvious the present claims. Thus, the skilled practitioner would not have a reasonable expectation of success to form the claimed conjugates when combining the method of Cervigni with the polyacetals of the '398 patent.

The Examiner considers the Applicant's arguments in the response filed August 4, 2008 regarding a reasonable expectation of success to be unpersuasive. The Examiner argues that polyacetals or polyketals are not labile under neutral pH, and that one of ordinary skill would be able to achieve the claimed conjugates by "choosing appropriate reaction conditions without undue experimentation, because they are known to one skilled in the art, and taught by many references." Applicant respectfully disagrees.

As an initial matter, Applicant respectfully submits that the stability of polyacetals or polyketals at neutral pH is not relevant to the Examiner's rejection. The rejection is over Cervigni in view of the '398 patent (and others), and the only pH exemplified by Cervigni is pH 3. Therefore, it is unclear how the stability of polyacetals or polyketals at neutral pH would be under consideration when combining the method of Cervigni with the polyacetals of the '398 patent. Rather, one of ordinary skill would consider the reactivity and stability of the polyacetals of the '398 patent under very acidic conditions, and the skilled artisan would not be motivated to pursue such a combination due to the known instability of PHF under acidic conditions.

Furthermore, it is well established that it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir.

1983). Here, the art clearly teaches that the biodegradable biocompatible polyacetal exemplified by the '398 patent is not stable at the pH taught by Cervigni. Thus, one of ordinary skill would not have a reasonable expectation of success of arriving at the claimed invention when applying acidic conditions to the biodegradable biocompatible polyacetals of the '398 patent.

Therefore, as argued in the Applicant's response filed August 4, 2008, the Examiner has failed to show why a skilled practitioner would be motivated to combine Cervigni with the '398 patent. Even if one were so motivated, Applicant respectfully submits that the Examiner has further failed to show how the skilled practitioner would have any reasonable expectation of success given the state of the art at the time of filing.

#### Double Patenting

Claims 1-12, 14, 19-22, and 41-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 29-42 of copending U.S. Pat. Appl. No. 10/501,565 (the '565 application). As stated in the previous response, Applicants hold this rejection in abeyance to be addressed when a relevant claim of the '565 application issues.

Applicants invite the Examiner to call their attorney, Brenda Herschbach Jarrell, at (617) 248-5175 with any questions pertaining to the above-identified application in order to expedite prosecution of this case.

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Respectfully submitted,

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